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Adverse Drug Reactions- Risk Factors, Epidemiology, and Management Strategies

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ABSTRACT

Objectives: The objective of this article is to review the impact of various factors on the occurrence of Adverse Drug Reactions (ADRs).

Summary: ADRs can be caused by several factors, including patient-related, drug-related, and social factors. Age is a crucial factor in the occurrence of ADRs, with both very young and very old patients being more vulnerable than other age groups. Alcohol consumption also plays a significant role in ADRs. Other factors that affect ADRs include gender, race, pregnancy, breastfeeding, kidney problems, liver function, drug dose and frequency, and many others. The medical literature has extensively documented the impact of these factors on ADRs. Taking these factors into account during medical evaluation enables healthcare professionals to choose the most appropriate medication regimen for their patients.

Conclusion: Various factors affect the occurrence of ADRs, some of which can be changed (such as smoking or alcohol consumption) while others cannot be changed (such as age or genetic factors). Understanding the impact of these factors on ADRs can help healthcare professionals to select the best medication for their patients and provide them with appropriate advice. Pharmacogenomics, a new and innovative science, emphasizes the genetic predisposition of ADRs, providing a new perspective in the drug selection decision-making process.

***KEYWORDS:** Adverse drug reactions; Impact; Drugs; Factors; Reaction*

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1. INTRODUCTION

Now a day's drugs have become a major part in day-to-day life because drugs play a major role in prevention and treatment of health complaints but also, they show heavy risks like adverse effects, drug interactions etc. which are nothing but DRUG RELATED PROBLEMS (DRPs). Adverse drug reactions (ADRs) have a major impact on health care system as they may reduce quality of life of patients, prolong the hospital stay, increase the health care cost, lead to hospital readmission, and increases the mortality and morbidity. We can reduce them by preventing the occurrence of ADRs. In USA the economic burden due to drug related mortality and morbidity was estimated as USD177.4 billion annually.

Adverse drug reactions: The WHO defines an ADR as one which is noxious and unintended, and which occurs in doses normally used in human for prophylaxis, diagnosis or therapy of disease or for modification of physiological function. Kitteringham et al. (1994) suggested that for most adverse reactions, particularly the idiosyncratic drug reactions, predisposition seems to be multifactorial, involving not only defects at multiple gene loci but also environmental factors such as concomitant infection or the use of other drugs for different diseases. The majority of ADRs occur because of the extension of the desired pharmacologic effects of a drug, often due to the substantial variability in the pharmacokinetics and pharmacodynamics seen among patients. Pharmacological, immunological, and genetic factors are involved in the pathogenesis of ADRs. Factors that predispose to pharmacological ADRs include dose, drug formulation,

pharmacokinetic or pharmacodynamic abnormalities, and drug interactions. The metabolic conversion of drugs to metabolite is now established as a requirement for many idiosyncratic drug reactions (Masubuchi et al., 2007). Increased levels of reactive drug metabolites, their impaired detoxification, or decreased cellular defense against reactive drug products appears to be an important initiating factor (Guengerich and MacDonald, 2007). Immunological and genetic factors may play a role in the reaction of the body toward the drugs given.

Torpet et al. (2004) suggested ethnic variations also play an important role in the development of ADRs. Evans (2005) found that some risk factors are consistent for all ADRs and across multiple therapeutic classes of drugs, while others are class specific. High-risk agents should be closely monitored based on patient characteristics (gender, age, weight, creatinine clearance, and number of comorbidities) and drug administration (dosage, administration route, number of concomitantdrugs).

Factors which might increase the possibility of the occurrence of ADRs include; extremes of age, gender, multiple drugs, disease state, past history of ADR or allergy, genetic factors, large doses and many other factors. Discontinuation of the drugs or changing doses may be an important factor in developing ADRs to certain drugs in certain populations especially the elderly.

Agency for Healthcare Research (2001) suggested another potential cause of ADRs can stem from the clinician's reluctance to treat with adequate doses of a drug for fear of causing drug toxicity. ADRs may be caused by errors in manufacturing, supplying, prescribing, giving, or taking drugs. Eighteen percent of drugs related to ADRs in the Harvard medical practice study were judged to be due to negligence, defined as failure to meet the standard of care reasonably expected of a physician qualified to take care of the patient in question (Leapeet al., 1991).

Factors affecting the occurrence of ADRs are subdivided into five groups; Patient related factors, Social factors, Drug related factors, Disease related factors and ADR related factors. Untreated indications: The patient has a medical problem that requires medication therapy (an indication for medication use) but is not receiving a medication for that indication.

2. HISTORY

Adverse drug reactions occur more frequently in hospitalized patients where multiple changes are being made in patient's medication regimens and lack of continuity of care may be accompanied. Of these cardiovascular patients are at high risk for developing drps because they are commonly present with co morbid conditions and are prescribed with multiple drug regimens. According to WHO guidelines the number of cases of cardiovascular cases will be increase from 29 million in the year 2000 to about 69 million cases in 2017. So, the chances of occurring drug related problems are more in such kind of patients. So in order to identify the drug related problems in such patients with cardiovascular diseases, this study has been carried out.

Among the factors that can contribute to occurrence of Adrs, the association between polypharmacy and the incidence of adrs has been widely proved in proved in previous studies. Polypharmacy is defined as the use of multiple medications by a single patient and is commonly observed among geriatric patients. According to previous studies ADR associated hospital admissions are observed more in patients receiving 4 or more drugs than the patients. In previous studies it has been reported that 5-15% of elderly patients suffer clinically significant adverse reactions due to Adrs, whereas the number of elderly patients exposed to a Adrs is estimated between 35 and 60%.

Many factors play a crucial role in the occurrence of ADRs, some of these are patient related, drug related or socially related factors. Age for instance has a very critical impact on the occurrence of ADRs, both very young and very old patients are more vulnerable to these reactions than other age groups. Alcohol intake also has a crucial impact on ADRs. Other factors are gender, race, pregnancy, breast feeding, kidney problems, liver function, drug dose and frequency and many other factors. The effect of these factors on ADRs is well documented in the medical literature. Taking these factors into consideration during medical evaluation enables medical practitioners to choose the best drug regimen.

3. PATIENT RELATED FACTORS

3.1. Age

All drugs can produce ADRs, but not all patients develop the same level and type of ADRs. Age is a very important factor which affects the occurrence of ADRs.

Elderly patients with multiple medical problems who are taking multiple drugs, those who have a history of ADRs, and those with a reduced capacity to eliminate drugs are at high risk for ADRs.

A study by Debellis et al. (2003) about the incidence and preventability of ADRs among older persons in the ambulatory setting concluded that ADRs are common and often preventable among older persons

in the ambulatory clinical setting. More serious ADRs are more likely to be preventable. Prevention strategies should target the prescribing and monitoring stages of pharmaceutical care.

Interventions focused on improving patient adherence with prescribed regimens and monitoring of prescribed drugs. Elderly and pediatric patients are particularly vulnerable to ADRs because drugs are less likely to be studied extensively in these extremes of age and drug absorption and metabolism are more variable and less predictable in both of these groups. Efforts are needed to predict and prevent the occurrence of ADRs in children (Bates et al., 2001).

Infants and very young children are at high risk of ADRs because their capacity to metabolize the drug is not fully evaluated. The following are some factors that might affect the development of ADRs in neonates (Clavenna and Bonati, 2008):

1. Neonates have immature renal tubular function when they are below the age of 8 weeks, avoiding digoxin, aminoglycosides, ACE inhibitors, NSAIDs is a must (De-gregori et al., 2009).
2. Physiologic hypoalbuminemia in neonates affects drug dosing. Caution is recommended when dealing with high protein binding drugs such as NSAIDs (Anderson and Lynn, 2009).
3. Neonates, have low body fat; they might be affected by fat soluble drugs (Ibáñez et al., 2009).
4. Increased anesthetic effects due to immature blood brain barrier at <8 weeks of age (Schoderboeck et al., 2009).
5. Predisposition to hypotension due to poor cardiac compliance and immature baroreceptors (Pellicer et al., 2009).

Older people are at high risk of developing an ADR for several reasons. They are likely to have many health problems and thus take several prescriptions and over the counter drugs.

As people get older, the liver loses the ability to metabolize drugs (Budnitz et al., 2007).

As people age, the amount of water in the body decreases and the amount of fat tissue relative to water, increases. Thus, in older people, drugs that dissolve in water reach higher concentrations because there is less water to dilute them, and drugs that dissolve in fat accumulate more because there is relatively more fat tissue to store them.

Also, as people age, the kidneys are less able to excrete drugs into the urine, and the liver is less able to metabolize many drugs. Jimmy and Padma (2006) in their study concluded that the incidence of ADRs among elderly adults and older adults was significantly higher than other age groups. They also elaborated that the type of ADR is different among age groups, type A reactions were more common among elderly adults (85.9%) and type B reactions were more common in adults (35%) compared to other age groups.

3.2. Gender

The biological differences of males and females affect the action of many drugs. The anatomical and physiological differences are body weight, body composition, gastrointestinal tract factors, liver metabolism, and renal function.

Women in comparison to men have lower body weight and organ size, more body fat, different gastric motility and lower glomerular filtration rate. These differences can affect the way the body deals with drugs by altering the pharmacokinetics and pharmacodynamics of the drugs including drug absorption, distribution, metabolism and elimination.

Gender plays a role in the effect on ADRs. A study of sex differences in ADRs to antiretroviral drugs indicates potential sex differences in the frequency and severity of ADRs to antiretroviral drugs (Ofotokun and Pomeroy, 2003).

Hepatic enzyme CYP3A4 is more active in females than males which lead to different effects on drug metabolism (El-Eraky and Thomas, 2003). They also suggested that women are more prone than men to develop torsade de pointes ventricular tachycardia during the administration of drugs that prolong cardiac repolarization.

Women aged 17–44 years have twice as many physician visits and hospital stays as men. When reproductive and other sex-specific conditions are excluded, the difference in hospital stay virtually disappears, but the difference in ambulatory care is still approximately 30%. After the age of 45, when all sex-specific conditions are excluded, women continue to have approximately 10–20% more physician visits, with men having a greater frequency of hospitalization (Ensom, 2000).In a north Indian study by Singh et al. (1998) on angiotensin converting enzyme inhibitors and cough, females had a higher incidence of cough compared to males (37.9% vs. 15.5%).

In Chinese populations, the metabolism of midazolam in women is more than in men due to the activity of CYP3A4 (Labbé et al., 2000).

Moreover, the pharmacodynamic differences between men and women are particularly seen with cardiac and psychotropic drugs. Chlorpromazine and

fluspirilene seem to be more effective in women than in men for the same dosage and plasma concentration (Bing et al., 2003).

Some drugs affect one sex without the other, e.g. colchicine which is used for the treatment of many diseases including Familial Mediterranean fever might affect fertility in males but not in females (Sternberg and Hubley, 2004). On the other hand, hepatic drug reactions are more common in females. It was estimated that the female gender is a risk factor for hepatotoxicity more than men (Rajani et al., 2004).

One of the most consistent observations in health research is that women report symptoms of physical illness at higher rates than men. Still unresolved is whether this is due to clinical differences in morbidity or disease severity, or to differences in the following: illness behavior – women are more likely than men to interpret discomfort as symptoms; symptom perception – women's attentiveness to body discomfort increases their perception of symptoms and evaluation of those symptoms as illness; or symptom reporting – women may be more likely to recall and report symptoms (Verbrugge, 1985; Ahmed et al., 2009).

3.3. Maternity Status

Pregnancy has an impact on drug treatment. Not only are women affected by the drug, but the fetus will also be exposed to ADRs of the drug. There are certain physiologic changes that occur during pregnancy which might affect drug pharmacokinetics and pharmacodynamics, these changes are; total blood volume increases by 30–40% (1500–1800 ml), extravascular volume increase during the 2nd and 3rd trimester which leads to decreased plasma concentration of iron and some drugs, renal function improves with a renal plasma flow increment of 30% and GFR increases 50%, serum protein 1–1.5 lower; thus renally excreted drugs would have an increased rate of excretion, cardiovascular changes are noted by an increase in cardiac output of about 32% due to an increased heart rate (10–15 bpm) and increased stroke volume, blood pressure is relatively constant. Motility, acidity and tone of GIT are decreased during pregnancy, and this might interfere with drug absorption or excretion and finally drug metabolism may be affected at certain stages of pregnancy (Duncombe et al., 2008).

Drugs during pregnancy might affect either the mother or the embryo or both. The impact of drugs on fetal organogenesis is crucial because it might lead to teratogenicity and Dysmorphogenesis (Pack et al., 2009).

Many drugs for example, antihypertensive drugs such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers pose a risk to the health and normal development of a fetus (Alomar and Strauch, 2010).

3.4. Fetal Development

The fetus, which is exposed to any drugs circulating in maternal blood, is very sensitive to drug effects because it is small, has few plasma proteins that can bind drug molecules and has a weak capacity for metabolizing and excreting drugs. Once drug molecules reach the fetus, they may cause teratogenicity (anatomic malformations) or other ADRs (Brundage, 2002). Gestational age is subdivided into three trimesters; first, second and third trimester.

The effect of drugs on each trimester is different depending on the degree of fetal development. Drug teratogenicity is most likely to occur when drugs are taken during the first trimester of pregnancy, when fetal organs are formed (Holmes et al., 2001). For drugs taken during the second and third trimesters, ADRs are usually manifested in the neonate (birth to 1 month) or infant (1 month to 1 year) as growth retardation, respiratory problems, infection, or bleeding. Overall, effects are determined mainly by the type and amount of drugs, the duration of exposure, and the level of fetal growth and development when exposed to the drugs. Both therapeutic and non therapeutic drugs may affect the fetus (Meloni et al., 2009).

3.5. Body weight and fat distribution

In the body, drugs are distributed to and from the blood and various tissues of the body (for example, fat, muscle, and brain tissue). After a drug is absorbed into the bloodstream, it rapidly circulates through the body. As the blood recirculates, the drug moves from the bloodstream into the body's tissues. Once absorbed, most drugs do not spread evenly throughout the body. Some drugs dissolve in water (water-soluble drugs), such as the antihypertensive drug atenolol. Some drugs tend to stay within the blood and the fluid that surrounds cells (interstitial space). Drugs that dissolve in fat (fat-soluble drugs), such as the anesthetic drug halothane, tend to concentrate in fatty tissues. Other drugs concentrate mainly in only one small part of the body (for example, iodine concentrates mainly in the thyroid gland), because tissues have a special attraction for (affinity) and ability to retain the drug. Drugs penetrate different tissues at different speeds, depending on the drug's ability to cross membranes. For example, the anesthetic thiopental, a highly fat-soluble drug, rapidly enters the brain, but the antibiotic penicillin, a

water-soluble drug, does not. In general, fat-soluble drugs can cross cell membranes more quickly than water-soluble drugs.

For some drugs, transport mechanisms aid movement into or out of the tissues (Anderson and Holford, 2008). Some drugs leave the bloodstream very slowly, because they bind tightly to proteins circulating in the blood. Others quickly leave the bloodstream and enter other tissues, because they are less tightly bound to blood proteins. Some or virtually all molecules of a drug in the blood may be bound to blood proteins. The protein-bound part is generally inactive. As the unbound drug is distributed to tissues and its level in the bloodstream decreases, blood proteins gradually release the drug bound to them. Thus, the bound drug in the bloodstream may act as a reservoir for the drug (Standing et al., 2010). Some drugs accumulate in certain tissues, which can also act as reservoirs of the extra drug. These tissues slowly release the drug into the bloodstream, keeping blood levels of the drug from decreasing rapidly and thereby prolonging the effect of the drug. Some drugs, such as those that accumulate in fatty tissues, leave the tissues so slowly that they circulate in the bloodstream for days after a person has stopped taking the drug (Zhao et al., 2009). Distribution of a given drug may also vary from person to person.

For instance, obese people may store large amounts of fat-soluble drug, whereas very thin people may store relatively little. Older people, even when thin, may store large amounts of fat-soluble drugs because the proportion of body fat increases with aging (Rhodin et al., 2009).

4. SOCIAL FACTORS

4.1. Alcohol drinking

Alcohol affects the metabolism of many drugs and it facilitates the development of ADRs. Alcohol drug interaction refers to the possibility that alcohol may change the intensity of the development of ADRs making it more toxic or harmful to the patient either in a pharmacokinetic or pharmacodynamic manner (Bruce et al., 2008). Taking alcohol with certain drugs can cause many ADRs like nausea, vomiting, headaches, drowsiness, fainting, loss of coordination, hypotension and many other ADRs (Krupski et al., 2009). Internal bleeding may occur due to severe ulceration if alcohol is taken with NSAIDs by a patient having peptic ulcer or ex-peptic ulcer or gastritis (Kim et al., 2009). Chronic alcohol consumption activates enzymes which transform some drugs into toxic chemicals that can damage the liver and other body organs. Alcohol can also magnify the inhibitory effects of sedatives and narcotics at their site of action in the brain.

4.2. Race and Ethnicity Factors

Evidence suggest that ethnicity exerts a substantial influence on drug response and action. Drug action varies greatly between individuals. Ethnic background is controlled by genetic factors, which makes the inter-individual differences due to polymorphisms in genes encoding drug metabolizing enzymes, drug transporters, and receptors (Sexton et al., 2000). Recent development suggests that ADRs may be avoided by individualizing the therapeutic plan according to genetics (Meigs et al., 2008). David et al., 2001) suggested genetics play a crucial part in the willingness of some patients to develop ADR for a specific drug over others. A study on epidemiological risk factors for hypersensitivity reactions to abacavir found the Caucasian race as a risk factor for ADRs (Lyssenko et al., 2008).

4.3. Smoking

Smoking is one of the risk factors of many diseases like peptic ulcer, cancer and cardiovascular diseases (Woo et al., 2009). It also affects the metabolic process by affecting liver enzymes acting as a potent inducer of the hepatic cytochrome P-450 (CYP) isoenzymes 1A1, 1A2, and, possibly, 2E1 (Tomlinson et al., 2005). Many drugs are substrates for hepatic CYP1A2, and their metabolism can be induced in smokers, resulting in a clinically significant decrease in pharmacologic effects (Faber and Fuhr, 2005). These drug interactions are not caused by nicotine, the cause is tobacco. Because it stimulates the sympathetic nervous system, nicotine can counter the pharmacologic actions of some drugs (Hukkanen et al., 2005). More research findings worldwide revealed the smoking-drug interaction, and theophylline, flecainide, insulin, oral contraceptives, beta-blockers, thiothixene and H2 blockers are medicines whose therapeutic responses can be affected by smoking (Himmelmann et al., 2003). One clinical study showed that on average insulin-dependent diabetic smokers needed 15–20% more insulin than non-smokers, and up to 30% more if they smoked heavily (Kroon, 2007). Cigarette smoking increases the rate of heparin clearance, possibly because of the smoking-related activation of thrombosis with increases of heparin binding to antithrombin III (Faber and Fuhr, 2005). Cutaneous vasoconstriction by nicotine may decrease the rate of insulin absorption after subcutaneous administration (Schwing et al., 1999).

5. CONCLUSION

Different factors affect the development of ADRs in different degrees, some of these factors have a direct effect on ADRs, others are insidious. Serious attention to these factors will result in preventing or

reducing the occurrence of unwanted drug actions which could have been avoided if health care providers spent enough time to pinpoint these problems. Health education, counseling and reconciliation are tools that must be utilized by pharmacists. Information technology should also be part of the medication decision making process which provides health professionals with up to date knowledge of drug-dosing, interaction, ADRs and other important information needed to use medication in the optimum manner. The elderly should also be the focus of the pharmacist, because they form the majority of those who uses polypharmacy. Finally; for each benefit to come out of a medication there is always a possibility for some risks; benefits should always out weight risks for the purpose of providing the best treatment with the least number of medications at the most economic price.

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